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August 31, 2004
Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

RE: NDA 21-695 Patent Certifications

CITIZEN PETITION

INTRODUCTION

On behalf of Abbott Laboratories ("Abbott") and Laboratoires Fournier, SA ("Fournier"), the undersigned submit this Citizen Petition pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 355 (2000); 21 C.F.R. § 10.25(a) (2004); and 21 C.F.R. § 10.30 (2004) to request that the Commissioner of Food and Drugs (the "Commissioner") reject New Drug Application ("NDA") 21-695 unless and until the sponsor, Reliant Pharmaceuticals LLC ("Reliant"), fulfills its statutory obligations by certifying to all patents properly listed for NDAs 21-203 and 19-304.

Reliant has submitted an NDA pursuant to FDCA § 505(b)(2) in an effort to obtain approval of its micronized fenofibrate capsule product by relying on investigations it does not own and as to which it does not have a right of reference or use. Reliant has indicated that its NDA relies on investigations owned by Fournier and licensed to Abbott and submitted to FDA by Abbott in support of NDAs for Abbott's fenofibrate products. Upon submission of its 505(b)(2) NDA, Reliant was required by section 505(b)(2) and 505(b)(2)(A) to certify as to all patents properly listed for any drug previously approved on the basis of the investigations on which NDA 21-695 relies.

Reliant certified to the patents listed for Abbott's NDA 19-304 (micronized fenofibrate capsules), but did not certify to those listed for Abbott's NDA 21-203 (fenofibrate tablets). This selective certification was not permissible because NDA 21-203 relied upon, and was approved by FDA based in significant part on, the same clinical and non-clinical investigations for fenofibrate contained in Abbott's NDA 19-304.

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A. ACTION REQUESTED

Abbott and Fournier ask FDA to reject Reliant's submitted NDA 21-695 and notify Reliant that it must include in any section 505(b)(2) NDA for the product covered by NDA 21-695 certifications with respect to the patents listed for NDA 21-203.

Abbott and Fournier ask FDA not to approve NDA 21-695 unless and until (i) Reliant makes all required patent certifications in that NDA; (ii) if those certifications are Paragraph IV certifications, Reliant provides appropriate notice to Abbott; and (iii) if, within 45 days of receipt of such notice, Abbott or Fournier files a patent infringement action against Reliant with respect to one or more of the patents addressed in the notice, until not earlier than 30 months (or such shorter or longer period as the patent court may order) after the date of receipt of the notice (or until a court decision of invalidity or non-infringement of each of the patents in litigation, if earlier).

B. STATEMENT OF GROUNDS

I. BACKGROUND.

Abbott, under license from Fournier, currently markets fenofibrate tablets pursuant to NDA 21-203, which FDA approved on September 4, 2001.

Previously, Abbott marketed a micronized fenofibrate capsule product pursuant to NDA 19-304, which FDA approved on February 9, 1998 (67 mg) and June 30, 1999 (134 and 200 mg). Marketing of micronized fenofibrate capsules was discontinued by Abbott upon approval of the tablet formulation in 2001, but the NDA was not withdrawn. An additional never-marketed non-micronized fenofibrate capsule product (100 mg) was approved under the same NDA on December 31, 1993.

Abbott's NDA 21-203 cross-referenced the nonclinical and clinical investigations, data and information previously submitted in NDA 19-304. All clinical studies used to support the safety and effectiveness of the two marketed fenofibrate formulations (tablets and micronized capsules) were performed using the never-marketed 100 mg capsules. In fact, all original clinical data submitted in NDA 21-203 were derived from a study in healthy subjects, which demonstrated the bioequivalence of fenofibrate tablets to the original (100 mg) fenofibrate capsules. Thus, approval of NDA 21-203 was based in large part on studies conducted by or for Abbott in connection with NDA 19-304.

By letter of February 18, 2004 (Tab 1), Reliant informed Abbott and Fournier that it had submitted a section 505(b)(2) NDA for micronized fenofibrate capsules (43 mg, 87 mg, and 130 mg) that cited as its reference listed drug the discontinued micronized fenofibrate 200 mg capsules for which Abbott holds the NDA. This letter also provided notice that Reliant had included in its application a Paragraph IV certification with respect to U.S. Patent No. 4,895,726 (the "'726 patent"), which was the patent listed in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book") for NDA 19-304.

In response, Abbott and Fournier notified Reliant that it is required to submit patent certifications as to each of Abbott's fenofibrate products approved on the basis of the investigations on which Reliant seeks to rely. Letter from Eugene M. Gelernter of Patterson, Belknap, Webb & Tyler to Andrew M. Berdon of Quinn Emanuel Urquhart Oliver & Hedges, LLP (March 16, 2004) (Tab 2). In particular, Abbott and Fournier stated that Reliant is required to submit certifications for all patents listed for Abbott's NDA 21-203, including U.S. Patent Nos. 6,074,670 (the "'670 patent"), 6,277,405 (the "'405 patent"), 6,589,552 (the "'552 patent") and 6,652,881 (the "'881 patent"). *Id.* at 1. Reliant has refused to submit these necessary certifications, erroneously claiming that "it was only required to file a certification of non-infringement with respect to the '726 patent." Letter from Andrew M. Berdon to Eugene M. Gelernter at 2 (March 19, 2004) (Tab 3).

While Reliant has refused to certify to the '670, '405, '552, and '881 patents, another similarly situated section 505(b)(2) applicant, Cipher Pharmaceuticals Ltd. ("Cipher"), which submitted a section 505(b)(2) application for fenofibrate capsules (50, 100, and 150 mg) similar to Reliant's, has certified as to those patents. Letters from Ian W. French, Cipher Pharmaceuticals, to Abbott Laboratories (March 5, 2003 ('726, '670, and '405 patents), August 18, 2003 ('552 patent), and Feb. 3, 2004 ('881 patent)) (Tabs 4, 5, 6). After a lawsuit against Cipher for patent infringement was initiated, consistent with the statutory regime, the Cipher product's approval by FDA was stayed for 30 months or until resolution of the patent case.

Indeed, Cipher signed a co-marketing agreement with Reliant in January 2003, under which Reliant will be the exclusive North American distributor for Cipher's fenofibrate product. *CML Healthcare Subsidiary Cipher Pharmaceuticals Concludes Distribution and Supply Agreement for Fenofibrate*, Cipher Press Release (Jan. 30, 2004) (Tab 7). Thus, as a practical matter, Reliant seeks to be the beneficiary of two inconsistent positions regarding the need to certify as to those patents.

On June 1, 2004, Reliant sued Abbott and Fournier for a declaratory judgment that its proposed micronized fenofibrate product does not infringe Abbott's and Fournier's patents, including both those listed under NDA 19-304 and those listed under NDA 21-203. *Reliant Pharms., Inc. v. Abbott Labs. & Laboratoires Fournier*, No. C.A. 04-350 (D. Del. filed June 1, 2004) (Tab 8). Reliant brought this declaratory action without having provided any of the required patent certifications for the patents listed in NDA 21-203. Abbott and Fournier have moved to dismiss Reliant's lawsuit.

II. ANALYSIS.

A. The Plain Meaning of § 505(b)(2)(A) Requires a Certification as to Each Patent that Claims a Drug for Which an Investigation Relied on in a § 505(b)(2) Application Was Conducted.

Section 505(b)(2) provides:

> An application submitted under paragraph (1) for a drug for which the investigations described in clause (A) of such paragraph and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted shall also include
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> (A) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for such drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under paragraph (1) or subsection (c) . . . .

FDCA § 505(b)(2).

As relevant here, the meaning of section 505(b)(2) and section 505(b)(2)(A) is plain. A section 505(b)(2) application relies on certain investigations that "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted." Those investigations were conducted "for" a certain drug. Certain patents

claim that drug and were submitted to FDA pursuant to section 505(b)(1) or (c). The section 505(b)(2) application is required to certify as to each such patent, *i.e.*, "each patent which claims the drug for which such investigations were conducted."

In the FDCA, the term "drug" is not limited to a particular drug product (*i.e.*, a finished dosage form), but also includes a drug substance, which is a component of a drug product. *See* FDCA § 201(g)(1)(D), 21 U.S.C. § 321(g)(1)(D) (2000). *See also, e.g., Premo Pharm. Labs., Inc. v. United States*, 629 F.2d 795, 799 (2d Cir. 1980) (21 U.S.C. § 321(g)(1)(B) ("encompasses drug products as well as active ingredients"); *Pfizer, Inc. v. FDA*, 753 F. Supp. 171, 176 (D. Md. 1990) ("This definition [21 U.S.C. § 321(g)(1)] covers both a finished 'drug product' and its active and inactive ingredient or ingredients.")

The critical statutory expression in section 505(b)(2)(A) – "each patent which claims the drug for which such investigations were conducted" – encompasses patents that claim the drug for which the investigations relied on were conducted. Plainly, the drugs on which investigations are conducted are the formulations and their individual components, including the drug substance. Equally plainly, the drugs for which investigations are conducted are those formulations and components and also future formulations whose approval the investigations may support.

Here, the investigations at issue include animal toxicology studies and clinical (*i.e.*, human) effectiveness studies, which were conducted on the drug substance, fenofibrate, and on the first developed, never marketed dosage form of that drug. Such studies were performed "for" any dosage form that the sponsor or a licensee may ultimately market. Those investigations were thus conducted for the particular drug products covered by NDAs 19-304 and 21-203 and, potentially, other fenofibrate drug products for which Abbott and Fournier might seek FDA approval. For example, those investigations were necessary to support FDA approval of NDA 21-203 for fenofibrate tablets, just as much as they were to support approval of the marketed capsules covered by NDA 19-304, even though the clinical investigations involved capsule formulations different from either of those marketed products. Thus, the investigations were conducted "for" the tablet formulations, just as they were conducted "for" the marketed capsule formulations.

Congress could have written the statute to require certification only as to patents covering the drug "on which" the investigations in question were performed. Had the statute been written that way, certification would be required only for patents on the drug substance used in the preclinical safety studies and the formulation used in the clinical trials. That is, however, not the way the statute is written. Reliant recognized

this by certifying as to the patent listed for the micronized capsule formulation approved under NDA 19-304, a patent that does not apply to either the active substance fenofibrate or the original non-micronized capsule formulation used in the clinical studies.

Reliant is required by sections 505(b)(2) and (b)(2)(A) to provide, as part of its 505(b)(2) application, a patent certification "with respect to each patent which claims the drug for which such investigations were conducted . . . and for which information is required to be filed" by an NDA applicant. FDCA Section 505(b)(2)(A). The investigations on which Reliant seeks to rely were performed for, and provide necessary support for, the approvals of NDAs 19-304 and 21-203. Therefore, Reliant is required to certify as to each patent that claims a product covered by and listed with respect to NDA 19-304 and as to each patent that claims a product covered by and listed with respect to NDA 21-203.

This analysis is confirmed by *Marion Merrell Dow, Inc. v. Hoechst-Roussel Pharmaceuticals, Inc.*, No. 93-5074 (AET), 1994 WL 424207 (D.N.J. May 5, 1994) (attached as Tab 9). There, Hoechst-Roussel ("H-R") submitted a section 505(b)(2) NDA for a sustained-release version of diltiazem. H-R relied on clinical studies it had conducted of the safety of its own sustained-release product. H-R also relied, however, on non-clinical investigations for the diltiazem drug substance that had been conducted by Marion Merrell Dow and relied upon to support the approval of its immediate-release diltiazem (NDA 18-602) and its sustained-release diltiazem (NDA 20-062).

As the case was presented to the court, the issue was whether section 505(b)(2) and (b)(2)(A) required H-R to certify as to the two patents that claimed Marion Merrell Dow's sustained-release product and were listed in the Orange Book for NDA 20-062 but not for NDA 18-602.[1]

H-R argued that it was not required to certify as to those patents because the investigations it relied on had been submitted to FDA in connection with Marion Merrell Dow's immediate-release product, and therefore those studies had not been

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[1] H-R had initially certified to the patents claiming Marion Merrell Dow's immediate-release form of diltiazem and also as to patents claiming the sustained-release formulation. H-R then "corrected" its certifications by withdrawing the certifications as to the patents that claimed the sustained-release product. With that "correction," H-R placed itself in the same position that Reliant is in here, *i.e.*, the position of certifying as to the listed patents for fewer than all the drug products containing the active ingredient that was the subject of the investigations relied on.

conducted for Marion Merrell Dow's sustained-release product. The court squarely rejected that argument:

> The section under scrutiny here modifies the word "drug" by "for which the investigations were conducted". 21 U.S.C. § 355(b)(2)(A). In H-R's own words it intended to rely upon the investigations for "*diltiazem itself*, which was [sic] already on file with the FDA *in connection with* the original NDA filed for immediate release diltiazem." (See Def.'s Br. at 2) (emphasis added). Hence the drug for which the investigations were conducted was diltiazem and not immediate release diltiazem. Therefore, any patent which covers diltiazem itself should have been listed by H-R in its certification. Any other construction of the statute would be contrary to its plain meaning and inconsistent with Congress' intent not only to provide the public with easier and faster access to new drugs, but also to protect those individuals who pioneered patented new drugs which are on file with the FDA.

1994 WL 424207 at *3 (emphasis in original). The court added:

> The Court notes that the investigations need not have been conducted for a particular patent in order for that patent to be included in the certification. A certification must include any patent which covers *a drug for which the investigations were conducted.*

Id. n.2 (emphasis in original). On the basis of this analysis, the court deemed H-R to have certified to all of the diltiazem patents and permitted Marion Merrell Dow to proceed with an infringement action as to all of the patents under 35 U.S.C. § 271(e)(1).

Similarly, here, the toxicological and human safety and efficacy investigations Reliant relies on were conducted for fenofibrate, the drug substance or active ingredient – not for any particular dosage form. This is confirmed by the fact that Abbott relied on the same investigations in its NDA for its capsule products (NDA 19-304) and its NDA for its tablet product (NDA 21-203).

The statutory context of section 505(b)(2) confirms this analysis. The term "such investigations" in section 505(b)(2)(A) refers to the "investigations described in [section 505(b)(1)(A)], and relied upon by the [section 505(b)(2)] applicant for

approval of the application [that] were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use." Investigations described in FDCA § 505(b)(1)(A) are "investigations which have been made to show whether or not [the drug covered by the NDA] is safe for use and whether such drug is effective in use; . . . ." 21 U.S.C. § 355(b)(1)(A). Such studies include both clinical investigations of a particular finished dosage form and non-clinical pharmacology and toxicology investigations, which, in almost all cases, would be conducted on the active ingredient in such carriers as would be necessary for the particular non-clinical study in question. *See* 21 C.F.R § 314.50(d)(2),(5) (2004). The purpose of such toxicology investigations is to assess the safety of the drug substance generally, not merely in the particular formulations used in those particular investigations. Thus, the investigations are conducted "for" the drug substance in all formulations to which the investigations may be scientifically relevant.

Here, the studies on which Reliant relies were conducted by or for Abbott and are scientifically relevant to both Abbott's NDA 19-304 and its NDA 21-203. In these circumstances, Reliant should be required to provide patent certifications for the patents relevant to both NDA's. Reliant is not entitled to pick and choose as between the patents for which certifications must be provided.

B. The Plain Meaning of § 505(b)(2) Serves Sound Public Policy.

The procedure for patent certification and subsequent infringement litigation before approval of an application with a paragraph IV certification is an important element of the protections the Hatch-Waxman Amendments accord to innovators, and directly furthers the goal of resolving patent disputes while the FDA approval process is ongoing. This procedure is a critical part of the balance the Amendments strike between the interests of innovators and those of generic manufacturers.

It is well recognized that, during the investigation of a drug under an investigational new drug exemption ("IND"), its formulation and even dosage form may well change. *E.g.*, CDER & CBER, *Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products* 5 (Nov. 1995). The certification requirement would provide little or no protection for innovator firms if, for example, a section 505(b)(2) application relies on animal toxicology investigations conducted on formulations never marketed and the 505(b)(2) applicant were required to certify only as to patents claiming those formulations.

The statute does not permit a Section 505(b)(2) applicant such as Reliant to pick and choose the patents on which it wants to certify, when all of the patents cover the drug for which investigations relied upon by the applicant were conducted by or for the innovator. Such a reading –apparently adopted by Reliant – stands the statutory protections of section 505(b)(2) on its head.

C. FDA Interprets § 505(b)(2) and (b)(2)(A) as Imposing a Broad Certification Requirement, Including Certifications as to Patents Claiming Any Product Containing the Relevant Drug Substance.

FDA has interpreted section 505(b)(2) and (b)(2)(A) as requiring certification:

> with respect to each patent issued by the United States Patent and Trademark Office that, in the opinion of the applicant and to the best of its knowledge, claims a drug (the drug product or drug substance that is a component of the drug product) on which investigations that are relied upon by the applicant for approval of its application were conducted. . . .

21 C.F.R. § 314.50(i)(1)(i)(A) (2004).

There is no suggestion in the preambles to the proposed and final versions of this regulation that FDA intended there to be any difference between the statutory expression "for which such investigations were conducted" (emphasis added) and the expression in the regulation, "on which investigations that are relied upon by the applicant for approval of its application were conducted" (emphasis added).[2] That the Agency intended no such difference is shown by the reference in section 314.50(i)(1)(i)(A) to "the drug product or drug substance that is a component of the drug product." By expressly recognizing that an investigation can be of a drug substance, the Agency made clear that investigations are not limited to the particular formulations or dosage forms used in them, or to any one particular dosage form whose approval an investigation supports.

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[2] *See* 54 Fed. Reg. 28,872, 28,890-92 (July 10, 1989); 59 Fed. Reg. 50,338, 50,339-41 (Oct. 3, 1994).

As the court in *Marion Merrell Dow* held, section 505(b)(2) and (b)(2)(A) require certification as to all patents covering drugs for which investigations relied on were conducted. Plainly, an innovator applicant conducts safety and effectiveness investigations of a drug substance as support for each dosage form of the drug it may ultimately develop. Here, Abbott and Fournier obtained approval of the currently marketed tablet formulation on the basis of both the preclinical safety investigations conducted on fenofibrate and the clinical investigations conducted on the original, never marketed 100 mg capsule formulation of fenofibrate. Consequently, those investigations were conducted for fenofibrate products generally, including the tablet dosage form.

Not even Reliant suggests that it need certify only as to patents claiming the particular formulations actually tested in the preclinical or clinical investigations. The patent listed for the discontinued capsule product, to which Reliant did certify, does not, by its terms, claim either the active ingredient used in the non-clinical investigations of fenofibrate or the original, never marketed, capsule product that was used in the clinical investigation that formed the basis for approval of fenofibrate. Just like the NDA for the tablet product, the NDA for the previously marketed micronized capsule product relied on the non-clinical investigations of fenofibrate and was linked, by bioequivalence testing, to the original unmarketed capsule product on which the clinical investigations were conducted.

FDA's Draft Guidance for Industry: Applications Covered by Section 505(b)(2) (Oct. 1999) ("Draft Guidance") states:

> If there is a listed drug that is the pharmaceutical equivalent of the drug proposed in the 505(b)(2) application, the 505(b)(2) applicant should provide patent certifications for the patents listed for the pharmaceutically equivalent drug.

Draft Guidance 8. The requirement to certify to patents on listed drugs that are pharmaceutically equivalent to the 505(b)(2) drug evidences FDA's rejection of the view that certification is required only as to patents that claim the drug formulations that were actually tested in the investigations relied on by the 505(b)(2) applicant.

The Draft Guidance also makes clear that this obligation to certify as to a "pharmaceutically equivalent" listed drug is in addition to, not a substitute for, the

statutory obligation to certify as to the patents on any drug for which the investigations relied on were conducted[3] *See id.*:

> A patent certification or statement as required under section 505(b)(2) of the Act with respect to any relevant patents that claim the listed drug and that claim any other drugs on which the investigations relied on by the applicant for approval of the application were conducted, or that claim a use for the listed or other drug (21 C.F.R. 314.54(a)(1)(vi)).

Draft Guidance 8 (emphasis added). The underlined language makes clear that the patents as to which certifications must be made in the section 505(b)(2) application are not limited to those that claim any particular listed drug. In light of the text of section 505(b)(2)(A), certifications must also be made as to patents that claim other drugs for which the investigations relied on by the applicant for approval of the application were conducted.

In the one situation of which we are aware that is apparently parallel to that presented by Reliant, FDA has in fact interpreted the statute in accordance with the plain meaning discussed *supra*. When Andrx submitted a 505(b)(2) application for an extended-release formulation of metformin, based on studies comparing its product to immediate-release metformin, FDA required Andrx to certify as to the patents covering the innovator's extended-release product. *See* "Andrx Fortamet Approved: Dosing Convenience Will Be Marketing Focus," *FDC Reports, "The Pink Sheet,"* May 3, 2004, at 16 (Tab 10); "Andrx Reports 2003 Fourth Quarter and Full Year Results," Business Wire 5 (Feb. 25, 2004) ("Though the Fortamet NDA used immediate release Glucophage as its reference listed drug, FDA recently advised the Company it must make a patent certification with respect to the Orange Book patents listed for Glucophage XR(R).") (Tab 11). The FDA's action recognizing the requirement that Andrx certify to the patents on the innovator's extended-release product appears to reflect the plain meaning of section 505(b)(2) and (b)(2)(A) discussed *supra*.[4]

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[3] Reliant's section 505(b)(2) NDA is for a different dosage strength than that of the discontinued capsule product covered by NDA 19-304 and is for a different dosage form from that of the tablet covered by NDA 21-203. Thus, the proposed Reliant product is not the pharmaceutical equivalent of any listed drug.

[4] Andrx's product had a dosage strength different from that of the innovator's extended-release product, and thus was not pharmaceutically equivalent to it. Consequently, the requirement to certify presumably was not based on the policy,

Footnote continued on next page

CONCLUSION

For all of the foregoing reasons, Reliant's section 505(b)(2) NDA cannot be approved because it lacks the required certifications as to patents listed for Abbott's NDA 21-203 that claim fenofibrate and compositions containing it, for which the investigations on which Reliant's NDA relies were conducted. Therefore, FDA should grant this Petition in all respects.

C. ENVIRONMENTAL IMPACT

The relief requested by this Petition would result in the refusal to approve a section 505(b)(2) application or a potential delay in that approval while statutory certification requirements are met (thus not changing the status quo). Because the grant of the Petition would not have an effect on the environment, no environmental assessment is required. 21 C.F.R. § 25.31(a).

D. ECONOMIC IMPACT

Information on the economic impact of the action requested by this petition will be submitted if requested by the Commissioner.

Footnote continued from previous page
discussed *supra*, relating to certifications as to patents on drugs that are pharmaceutically equivalent to a listed drug.

E. CERTIFICATION

The undersigned certify that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.

Respectfully submitted,

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